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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/402,488	**Applicant(s)** MOLONEY ET AL.	
	Examiner David J. Steadman	**Art Unit** 1656	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 October 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): see attachment.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,4-10,12-16,18,19,50 and 51*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see atachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: Notice of References Cited (Form PTO-892).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit: 1656

[1] Claims 1, 4-10, 12-16, 18-19, and 50-51 are pending in the application.

[2] Applicant's after-final amendment to the claims, filed 11 October 2006, is acknowledged and has been entered into the record. This listing of the claims replaces all prior versions and listings of the claims. The request for reconsideration in the amendment filed 11 October 2006 is acknowledged. While the amendment is sufficient to overcome the rejection of claims 4 and 48-49 under 35 U.S.C. 112, second paragraph, and the rejection of claims 10 and 16 under 35 U.S.C. 103(a), the claims are not in condition for allowance for reasons that follow.

[3] The rejection of claim 4 as lacking antecedent basis in the recitation of "said aspartic protease of step c)" is withdrawn in view of the amendment to claim 4.

[4] The rejection of claims 48-49 as being confusing is withdrawn in view of the amendment to cancel the claims.

[5] The new matter rejection of claims 1, 4-10, 12-16, 18-19, and 50 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the law does not require *in haec verba* support for the recited limitation of "non-human host cell." Applicant points out sections of the MPEP, which address negative limitations and descriptive support thereof, noting that "'there is nothing inherently ambiguous or uncertain about a negative limitation'" and "the 'fundamental factual inquiry' for written description 'is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now

claimed.'" According to applicant, the rejection fails to provide reasoning "why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention." Applicant argues the specification provides "ample support" for the recitation of "non-human host cell," pointing to p. 7, lines 3-4 and p. 13, lines 27-29 of the specification as supporting disclosure. Applicant argues that "when read in view of the disclosure as a whole," a skilled artisan would recognize that applicant was in possession of the claimed invention at the time of filing.

Applicant's argument is not found persuasive. The examiner acknowledges the specification's disclosure that "[t]he recombinant expression of vectors of the invention can be designed for expression of the encoded fusion proteins in prokaryotic or eukaryotic cells. For example, fusion proteins can be expressed in bacterial cells such as E. coli, insect cells..., yeast cells, plant cells, or mammalian cells" (specification at p. 7, lines 1-4) and that "[t]he fusion protein and/or mature protein may also be produced in an edible food source, such as animal milk or in an edible crop, which may be consumed without a need for further purification" (specification at p. 13, lines 27-29), acknowledges the recitation of "non-human host cell" is neither ambiguous or uncertain, and acknowledges the law does not require *in haec verba* support for a claim limitation. However, the examiner maintains the position that the application as filed fails to support the limitation of "non-human host cell" in claim 1. As noted in the prior Office action and undisputed by applicant, the recitation of "non-human host cell" is a negative limitation, which excludes a "human" host cell from the claimed invention. As noted in a prior Office action, according to MPEP 2173.05(i), "[a]ny negative limitation or

exclusionary proviso must have basis in the original disclosure" and notes that "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims...The mere absence of a positive recitation is not basis for an exclusion." According to MPEP 2163.I.B, "[w]hile there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." In this case, the examiner can find no "express, implicit, or inherent disclosure" in the specification to exclude a "human" host cell from the claims. While a positive disclosure of a "human" host cell for recombinant protein production in the specification may provide a basis for excluding a "human" host cell in claims, the examiner can find no such positive disclosure of recombinant protein production using a "human" host cell and applicant has made no attempt to point out such supporting disclosure. As such, in the absence of "express, implicit, or inherent disclosure" to exclude a "human" host cell from the claims, the limitation of "non-human host cell" is considered to be new matter.

[6] The scope of enablement rejection of claims 1, 4-10, 12-16, 18-19, and 50-51 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the Office action improperly focuses on "gene transfer," asserting that "recombinant protein production per se is not the focus of the invention." According to applicant, the specification is not required to provide detailed teachings and examples of recombinant protein production in various host cells, allegedly because that information was well-known to a skilled artisan at the

time of filing and supported by the cited references. Applicant argues that the examiner's references, which support lack of an enabling disclosure, do not show that undue experimentation is required. Instead, applicant argues these references actually support the position that the specification enables the full scope of the claims. Applicant argues the examiner's cited references fail to support a position of unpredictability, noting that the teachings of Dyck are "purely commercial considerations that have no bearing on the enablement of the claimed methods," that Dyck et al. teaches transgenic recombinant protein production in milk and pig blood and further teaches that transgenic calves, mice, rabbits, pigs, cattle, and poultry have been produced, that the teachings of Vain were taken out of context, and Potrykus is related to commercial considerations and is a subjective discussion. Applicant argues there is no requirement for a commercially viable embodiment, only that there is an enabling disclosure.

Applicant's argument is not found persuasive. It should be noted that the specification makes clear and applicant acknowledges that the scope of the claimed invention is intended as encompassing recombinant protein production in a transgenic animal or plant (*e.g.,* specification at p. 13, line 37 to p. 14, line 2). Thus, in order to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, the specification should enable the full scope of the claimed invention, which encompasses recombinant protein production using any “non-human organism” (claim 1) or any plant (claim 51). There is no dispute that methods for producing transgenic animals and plants were known in the prior art at the time of the invention. The issue at hand is whether the specification in view of the state of the art provides sufficient guidance to enable a

skilled artisan to make the full scope of the claimed invention. While applicant asserts the teachings of the cited references regarding the unpredictability in the art "address issues that have arisen as recombinant protein production has moved out of the research laboratory into the commercial world" and are "purely commercial considerations," there is nothing in the references that would indicate that the cited teachings are limited to or directed solely to commercial considerations and do not relate to the enablement of, *e.g.*, making a transgenic animal, and it is noted that the authors themselves appear to be university researchers, not "commercial" entities. Put another way, it would appear that the teachings of the cited references would apply to making a transgenic plant or mammal as encompassed by the claims and are valid in determining the state of the art at the time of the invention (and even after the invention as Dyck et al. and Vain et al. were published well after the time of the invention). In this case, the examiner is not requiring that the specification enable a "perfected, commercially viable embodiment." Instead, the examiner is requiring that the specification enable the full scope of the claimed invention as required by 35 U.S.C. 112, first paragraph. It is noted that applicant asserts the teachings of Vain et al. are taken out of context and that the statement "transgene expression in plants remains largely unpredictable" is directed to variation in expression levels and stability between independently transformed plants. The examiner acknowledges that the cited teaching of Vain et al. is not the entire sentence from which it is taken. However, it appears that it is applicant and not the examiner who has taken the teaching of Vain et al. out of context as Vain et al. teaches that "transgene expression in plants remains largely

unpredictable, and there is considerable variation in expression levels and stability between independently transformed plants" (emphasis added, p. 878, right column, top). As such, these statements appear to be independent, *i.e.,* the unpredictability referred to by Vain et al. is not limited to the variation in expression level and stability of transformed plants. While applicant notes that Potrykus presents a "subjective" discussion, a skilled artisan would recognize that any prior art reference is "subjective" to an extent, presenting views of the author, and it is noted that the reference of Potrykus appears to be based on objective evidence. While applicant argues that the ability to produce recombinant proteins in certain animals or plants was advanced at the time of the invention, it is noted that the claims are not so limited, and encompass recombinant protein production in *any* non-human host or plant host. For example, the claims encompass recombinant protein production via transgenesis in the chick, and Sang (*Mech. Dev.*, 121:1179-1186, 2004) acknowledges that transgenesis techniques in poultry species, such as chick, were highly underdeveloped (see, *e.g.,* p. 1179, left column and p. 1184, right column, bottom), even after the time of the instant invention. See also Mozdziak, *Dev. Dynam.* 229:414-421, 2004 for additional review. Even assuming *arguendo* the specification provided guidance for transgenically producing the fusion protein in any non-human organism, claims 10, 12, 16, and 18 encompass cleavage of the protein, after obtaining the fusion protein, in the milk, the stomach, *and* the gut of an animal, however, neither the specification nor the claims provides guidance regarding how the "fusion protein" is delivered intact to "the milk, the stomach, or the gut of an animal" without degradation of the fusion protein. Also, even assuming

arguendo the specification provided guidance for transgenically producing the fusion protein in any plant, regarding claim 51, neither the specification nor the prior art provides guidance or an expectation that the fusion protein will be cleaved *in vivo* by co-expression of an aspartic protease in a plant. In essence, the cited references support the examiner's position that there was unpredictability in generating a transgenic non-human animal or a transgenic plant at the time of the invention, which the disclosure of the specification fails to remedy, either by working examples, specific guidance, or a combination thereof. It should be noted that the level of unpredictability as evidenced by the cited references is only one of the Factors of *In re Wands* that has been analyzed by the examiner in previous Office actions. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of required experimentation, it is the examiner's position that undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

[7] The rejection of claim(s) 1, 4, 6-9, 13, 15, 19, and 51 under 35 U.S.C. 103 (a) as being unpatentable over Ward et al. in view of Walsh et al. and Yonezawa et al. is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant maintains the previously presented argument, re-stated herein as follows. Applicant argues the rejection is based on the incorrect assumption that chymosin will cleave any fusion protein at a Phe-Met junction.

Applicant refers to the Moloney Declaration, which explains that the prior art references of Visser et al., which is cited by Walsh et al., and Schettenkerk et al., which is cited by Visser et al., disclose that a minimum chain length of five amino acids residues including a Ser-Phe-Met-Ala is required for cleavage of a κ-casein polypeptide. Applicant also points to the Moloney Declaration explaining that in Figures 1 and 2 and the working examples that chymosin cleavage occurred between a Phe-Val and a Phe-Ser bond, respectively. In view of this evidence, applicant asserts the Moloney Declaration, the prior art, and the application data demonstrate that chymosin does not cleave all Phe-Met bonds. According to applicant, because one of ordinary skill in the art would not have expected chymosin to cleave all fusion proteins at a Phe-Met bond, the cited references fail to teach the claimed invention.

Applicant's argument is not found persuasive. It is noted that applicant is arguing against a limitation that is not present in the claims – the examiner cited Phe-Met as a representative example of a likely fusion site between a chymosin pro-peptide and a recombinant protein of interest. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

There appears to be no dispute that Ward et al. teaches a chymosin pro-peptide, which has Phe at its C-terminus, as a cleavable linker sequence of a fusion protein, Walsh et al. teaches the use of chymosin for cleavage of a fusion protein at a Phe-Met junction, and Yonezawa et al. teaches that chymosin *can* cleave, among others, a peptide having a Phe-Met junction. Applicant's position appears to be that chymosin

does not cleave at all Phe-Met bonds. The examiner does not dispute applicant's assertion. However, that the prior art teaches that chymosin does not cleave at any Phe-Met junction does not by itself obviate the instant rejection.

At the time of the invention, the prior art regarding preferred cleavage sites for chymosin was well-developed as evidenced by the references of Yonezawa et al. and Walsh et al. and also by references cited by Walsh et al., namely those of Visser et al. and Schettenkerk et al. Thus, if a direct fusion of a chymosin pro-peptide fused to a recombinant protein of interest is not amenable to cleavage by chymosin, one of ordinary skill in the art, in view of the available known cleavage sites for chymosin as taught by the prior art, could have readily engineered a cleavage site for a chymosin pro-peptide fused to a recombinant protein of interest with an expectation of successfully cleaving the pro-peptide from the recombinant protein of interest, particularly in view of the successful cleavage at a Phe-Met junction as shown by Walsh et al. and Yonezawa et al. Even applicant acknowledges that such experimentation was routine in the art at the time of the invention. In the response filed on 1/27/2003, applicant asserted that it is routine in the art to select a pro-peptide from any aspartic protease, fuse that pro-peptide to any recombinant protein of interest, and use any aspartic protease to cleave at the fusion protein junction (response filed on 1/27/2003 at pp. 3-5). As such, one of ordinary skill in the art would have had a reasonable expectation of success for fusing a chymosin pro-peptide to a recombinant protein of interest having an appropriate chymosin cleavage site and using chymosin to cleave at the fusion protein junction.

At least for the reasons of record and the reasons stated above, the examiner maintains the position that the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention.

[8] The rejection of claim 5 under 35 U.S.C. 103 (a) as being unpatentable over Ward et al. in view of Walsh et al. and Yonezawa et al. as applied to claims 1, 4, 6-9, 13, 15, 19, and 51 above, and further in view of Fine et al. is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant maintains the previously presented argument, re-stated herein as follows. Applicant argues the combination of Ward et al., Walsh et al., and Yonezawa et al. fail to teach or suggest the claimed invention and the reference of Fine fails to remedy this failure.

Applicant's argument is not found persuasive. At least for the reasons set forth above, the examiner maintains that the references of Ward et al., Walsh et al., and Yonezawa et al. teach the invention of claims 1, 4, 6-9, 13, 15, and 19 and in view of the additional teachings of Fine et al., the invention of claim 5 would have been obvious to one of ordinary skill in the art at the time of the invention.

[9] The rejection of claim(s) 10 and 16 under 35 U.S.C. 103 (a) as being unpatentable over Ward et al. in view of Walsh et al. and Yonezawa et al. as applied to claims 1, 4, 6-9, 13, 15, 19, and 51 above and further in view of evidentiary references Huber (US Patent 4,180,559) and Fan (US Patent 4,774,183) is withdrawn in view of the amendment to claims 10 and 16 to require that step d) be "effected in vivo."

According to an online dictionary definition, the term "*in vivo*" means "existing or carried out inside a living organism" (encarta.msn.com, last visited 31 October 2006). As such, the examiner has interpreted the claims as requiring that the "contacting" step of part d) of claim 1 is effected "inside a living organism."

[10] The rejection of claims 14 and 50 under 35 U.S.C. 103 (a) as being unpatentable over Ward et al., Walsh et al., and Yonezawa et al. as applied to claims 1, 4, 6-9, 13, 15, 19, and 51 above and further in view of Dunn et al. is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant maintains the previously presented argument, re-stated herein as follows. Applicant argues the combination of prior art fails to teach the claimed invention. Applicant argues that, although mature aspartic proteases have been shown to cleave specific peptides at specific sites, this does not implicate the use of a mature aspartic protease for cleaving the recited fusion protein. Applicant maintains the position that the rejection is based on hindsight reasoning because a skilled artisan would not expect that a fusion protein as recited in the claims could be cleaved by an aspartic protease without also incurring undesired cleavage. Applicant argues that without an assurance of accurate cleavage, there would have been no motivation to use an aspartic protease to cleave the fusion protein.

Applicant's argument is not found persuasive. As noted above, the invention of claim 1 is obvious in view of the combination of Ward et al., Walsh et al., and Yonezawa et al. and in view of the teachings of Dunn et al., the invention of claims 14 and 50 is

obvious. In view of the combined teachings of the cited references, one of ordinary skill in the art would have had a *reasonable* expectation of success that chymosin can cleave its own fusion protein when fused to a recombinant protein of interest. While applicant maintains that one would not know whether chymosin would non-specifically cleave a fusion protein and one would not expect to achieve accurate cleavage, the claims are not limited to specific or accurate cleavage of a fusion protein. As such, applicant is arguing a limitation that is not present in the claims. See MPEP 2145 regarding arguing limitations that are not claimed. In this case, it appears that applicant's current argument appears to contradict applicant's previous statements of record, which clearly support non-specific cleavage of the fusion protein being encompassed by the claimed method. For example, applicant has previously argued that "the claims do not preclude some non-specific cleavage of the heterologous protein" (response filed on 9/18/2001 at p. 6, bottom). In the same response, applicant states, "[a]pplicant has tested many proteins and has not observed *substantial* non-specific cleavage of any of the proteins" (italics added for emphasis, response filed on 9/18/2001 at p. 7, top), thus suggesting that at least *some* non-specific cleavage has been observed.

MPEP 2143.02 makes clear that absolute predictability is not required, only *some* degree of predictability. In view of the teachings as described above, one of ordinary skill in the art at the time of the invention would have had at least *some* degree of predictability that the fusion protein as taught by Ward et al. could be cleaved by an

autocatalytically maturing aspartic protease other than chymosin, *e.g.*, pepsin, particularly in view of the teachings of Dunn et al.

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER